REMARKS

Applicants are concerned that the prosecution of the subject application has regressed and before responding to the current Office Action feel compelled to summarize the previous course of examination for the record.

BACKGROUND

On September 5, 2001, the now-pending co-therapy claims were first presented for examination in response to a restriction requirement, which applicants found confusing. In the response (Amendment A), applicants also cited U.S. 6,245,797,which issued on June 12, 2001, claiming a method for reducing the risk of developing atherosclerotic disease by using a combination of an HMG-CoA reductase inhibitor and a COX-2 inhibitor.

Following an interview with Examiners Jagoe and Rose and upon responding to an Office Action issued on November 8, 2001, applicants in Amendment B, filed January 30, 2002, asked for reconsideration of their co-therapy claims embracing the prophylactic treatment of a subject at risk of developing a cardiovascular disorder by treating the subject with a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-acceptable salt thereof in combination with a lipid lowering drug. Dependent claims defined the lipid lowering drug as being selected from the group consisting of (1) an IBAT inhibitor, (2) a fibrate, (3) niacin, (4) a statin, (5) a CETP inhibitor and (6) a bile acid sequestrant. At the interview and following an exposition of the antecedent support for the claim language, the Examiner indicated that a 35 USC 112, paragraph 2 rejection would be withdrawn. At the interview and in the response, it also was urged that in view of the issuance of the '797 patent, the subject matter embraced by applicants' then-pending claims had already been considered to be patentable by the USPTO and thus were patentable over the cited combination of documents.

The possible need for instituting an interference with the '797 patent also was discussed during the interview.

Following the submission of Amendment B, Examiner Jagoe, on April 23, 2002 (Paper No. 16), issued a Communication setting a one-month shortened statutory period for response. The Communication did not consider Amendment B fully responsive to the November 2001 Office Action, stating that the rejection of Claims 1-39 as being unpatentable, under 35 USC 103(a), over Searle WO 95/15316 in view of the Merck Manual needed to be addressed. Applicants submitted Amendment C on May 18, 2002 in response. The Office Action had asserted that the WO publication taught that "COX-2 inhibitors would be useful for conditions such as vascular disease and myocardia ischemia and the like (citing page 7, lines 8-36)." The Office Action further asserted that the cited Merck Manual taught that "HMG-CoA reductase inhibitors (statins) can lower LDL levels and prevent unstable angina and MI and decrease the need for surgical coronary revascularization." According to the Office Action, "[i]t is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose" implying implicitly that the invention defined by the pending claims was nothing but such an obvious combination. In Amendment C, applicants argued that these cited documents did NOT teach that the separate compositions recited in the pending claims were useful "for the very same purpose" a linchpin for the Office Action's rejection. The Office Action jumped to this conclusion without any critical analysis of the actual teachings of the cited documents. Furthermore, neither of the cited documents provided a valid basis for its combination with the other. The combination posed by the Office Action, thus it was argued, resulted from an improper hindsight evaluation of the invention defined by the pending claims.

In a supplemental Amendment D, filed May 23, 2002, applicants added claims parallel to those then-pending and reciting (1) a method for preventing onset of a pre-clinically evident stage of a cardiovascular disorder in a subject at risk of developing a cardiovascular disorder; (2) a method for preventing onset of a clinically evident cardiovascular disorder in a subject at risk of developing a cardiovascular disorder and (3) a method for treating a subject at risk of developing a cardiovascular disorder. These claims were effectively transferred from applicants' co-pending application, S.N. 09/946,623.

THE CURRENT OFFICE ACTION

THE RESTRICTION REQUIREMENT

Notwithstanding the examination of both the method and composition claims in the Office Action of November 8, 2001, the Office Action now makes another restriction requirement; this time dividing the claims into a first group (Group I) directed to the various therapeutic methods (claims 13, 15-24, 26-31 and 40-68) and a second group (Group II) directed to therapeutic compositions (claims 32 and 34-39).

Applicants hereby elect the method claims of Group I with traverse.

The Office Action contends that the Groups I claims and Group II claims "do not relate to a single inventive concept under PCT Rule 13.1 because "the methods of group I are separate and distinct from the compounds of group II and each require a separate search." The reasoning supporting restriction is circular, at best, and in view of the fact that both groups were previously searched, the assertion of the need for a separate search seems disingenuous. Both sets of claims (Group I and Group II) contain the unifying thread of requiring a combination of "a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-

acceptable salt thereof in combination with a lipid lowering drug." The presence of this unifying thread shows that the method claims and the composition claims are not separate and distinct. In addition, the assertion of "serious undue burden" for the search and examination is simply not warranted. Both claim sets were previously searched and examined and the common aspect of both claim sets was the focus of the search and examination.

Furthermore, the United States Patent and Trademark Office has previously issued a patent, U.S. 6,245,797 (see above Background), containing both method and composition claims of a similar content. The issuance of such claims in a single patent is additional evidence against the correctness of restriction in this case. Withdrawal of the requirement for restriction is requested.

The Office Action also asks that a single species be elected. The nature of this request in the context of the pending claims is not fully understood. Nonetheless, in the spirit of advancing prosecution, applicants elect atherosclerosis as the cardiovascular disorder, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide as the cyclooxygenase-2 inhibitor and a statin as the lipid lowering drug.

All but claims 23, 31, 39, 48, 58 and 68 read on this combination (species).

THE SUBSTANTIVE REJECTIONS

Claims 40-58 were rejected under the first paragraph of 35 U.S.C. 112 as containing subject matter not described in the application. This rejection is respectfully traversed.

The Office Action argues that the recitations of "preclinically evident" and "clinically evident" are lacking. In this regard, the Office Action only refers to the description on page 29 of the application, completely ignoring the discussion on page 3. As described on page 3 of the

application (line 1 *et seq.*), the invention is directed to preventing cardiovascular disorders in a subject in need of such prevention. Further in the discussion (line 23 *et seq.*), "prevention" is defined as "preventing the onset of clinically evident cardiovascular disorders altogether or preventing the onset of a preclinically evident stage of cardiovascular disorder in individuals. This includes prophylactic treatment of those at risk of developing a cardiovascular disorder." The language of the claims is clearly supported. Those skilled in the art well-understand the changes in cardiovascular function and related symptoms indicative of either a preclinically evident disorder or a clinically evident disorder. The rejection should be withdrawn.

The Office Action also repeats the 102(b) rejection over the Searle PCT, a rejection that was previously overcome. The rejection is again traversed.

All of the pending claims require a combination of (1) a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-acceptable salt thereof and (2) a lipid lowering drug. The Searle PCT does not disclose the use of a lipid lowering drug for any purpose whatsoever, so the Searle PCT cannot anticipate the pending claims.

The Office Action also repeats the 103(a) rejection based on a combination of the Searle PCT and the Merck Manual. No acknowledgment of applicants' prior response was provided, let alone any discussion of why the explanation of how the rejection fails to present a *prima facie* case was lacking. In any event, the rejection is again traversed.

The prior issuance of U.S. 6,245,797 underscores the patentability of the subject matter embraced by applicants' pending claims, since substantially that same subject matter had already been considered to be patentable by the USPTO (in the issued '797 patent) and thus must be patentable over the cited combination of documents. The same combination of documents cited in the present Office Action would be prior art to the '797 patent. Indeed, the possible need for

instituting an interference between the '797 patent and the pending application was specifically discussed.

The similarities of the claimed subject matter to the invention claimed in the '797 patent is unmistakable. As described in prior Amendment A, U.S. 6,245,797, *inter alia*, claims a method for reducing the risk of developing atherosclerotic disease by using a combination of an HMG-CoA reductase inhibitor and a COX-2 inhibitor. HMG-CoA reductase inhibitors are also known as statins. By virtue of the April 18, 1997 filing date of applicants' provisional application, the '797 patent is not citable against the subject application as prior art under §§102 and 103 of the Patent Statute. As especially shown by a comparison of pending claim 24 and issued claim 1 of the '797 patent, the two inventions are substantially indistinguishable.

On the basis of the prior issuance of the '797 patent, applicants again assert that the pending claims should be found patentable over the cited combination of documents. In addition and as explained in more detail below, the claims also should be found patentable because the cited combination **simply does not present a valid prima facie case for obviousness**.

A prior Office Action acknowledged that the "claims are drawn to prophylactic treatment of a subject at risk of developing a cardiovascular disorder comprising treating a subject with a COX-2 inhibitor and *inter alia* a lipid lowering drug as a statin." The earlier Office Action asserted that the WO publication teaches that "COX-2 inhibitors would be useful for conditions such as vascular disease and myocardia ischemia and the like (page 7, lines 8-36)." The Office Action further asserted that the cited Merck Manual "teaches that HMG-CoA reductase inhibitors (statins) can lower LDL levels and prevent unstable angina and MI and decrease the need for surgical coronary revascularization."

The Office Action then argued that "[i]t is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose" implying implicitly that the invention defined by the pending claims is nothing but such an obvious combination. However, the cited documents do **NOT** teach that the separate compositions recited in the pending claims are useful "for the very same purpose." The Office Action jumped to this conclusion without any critical analysis of the actual teachings of the cited documents. Furthermore, neither of the cited documents provides a valid basis for its combination with the other. The combination posed by the Office Action has resulted from an improper hindsight evaluation of the invention defined by the pending claims. For these reasons, the rejection based on Section 103 must be withdrawn.

WO 95/15316 teaches that the recited compounds, a particular class of selective COX-2 inhibitors, are useful for the treatment of **inflammation** (page 7, lines 8-10). The cited WO publication specifically teaches that "[c]ompounds of Formula I would be useful in **treating inflammation** in such diseases as vascular diseases ... myocardial ischemia and the like" (page 10, lines 27-36). It was on the basis of this disclosure that the Office Action apparently asserted, as reported above, that the WO publication teaches that "COX-2 inhibitors would be useful for conditions such as vascular disease and myocardia ischemia and the like (page 7, lines 8-36)." This assertion in the Office Action, however, is an improper and incorrect over-generalization of the actual teachings of the document. As noted, the document merely teaches that such compounds are useful for treating **inflammation** associated with such conditions – not that the compounds are useful for treating the condition itself. The jump from the treatment of

inflammation to the treatment of the disease itself is simply unsupported by any valid interpretation of the WO publication.

Since, properly interpreted, the WO publication does not remotely suggest that the illustrated compounds can be used to treat either vascular disease, or myocardia ischemia, the WO document also provides absolutely no motivation for using such compounds for prophylactically treating a subject at risk of developing a cardiovascular disorder. Surely, there is no evidence in the present record that a subject at risk of developing a cardiovascular disorder needs to be treated for inflammation.

The independent claims of the pending application, claims 13, 24, 32, 40, 49 and 59 are specifically directed to the "prophylactic treatment of a subject at risk of developing a cardiovascular disorder," to the prevention of "atherosclerosis in a subject at risk of developing atherosclerosis," to "a pharmaceutical composition," to "preventing onset of a pre-clinically evident stage of a cardiovascular disorder," to "preventing onset of a clinically evident cardiovascular disorder" and to "treating a subject at risk of developing a cardiovascular disorder," respectively, each characterized by requiring a combination of a COX-2 inhibitor and a "lipid-lowering drug." The cited WO publication simply contains NO teaching that would make it obvious to use a COX-2 anti-inlfammatory drug in such instance, let alone in combination with the required "lipid-lowering drug."

The citation to the Merck Manual does not remedy any of the shortcomings of the cited primary reference.

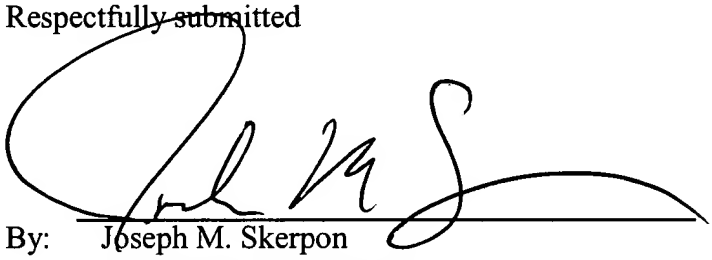
The Merck Manual was cited for its purported teaching "that HMG-CoA reductase inhibitors (statins) can lower LDL levels and prevent unstable angina and MI and decrease the need for surgical coronary revascularization." This teaching, however, does NOT provide any

basis on which the cited combination can be justified. There is simply no connection between the anti-inflammatory activity of the recited compounds of the WO publication and the LDL lowering activity of the statins described in the Merck Manual. In the absence of such a nexus, there is simply no motivation for using a combination of an anti-inflammatory and a lipid-lowering drug.

The Office Action selected these references purely from a hindsight consideration of applicants' pending claims. This is improper. The Office Action's only justification for selecting these disparate disclosures for consideration in combination was that they each teach compositions to be useful for the same purpose. That justification is purely and simply incorrect. The compositions of the respective documents are NOT taught to be useful for the same purpose. It is black letter law that a combination constructed from hindsight does not present a prima facie case of obviousness.

Consequently, based on the above, prompt reconsideration and full allowance of the claims pending in the subject application are respectfully requested.

Respectfully submitted



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